CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA
1-BROMO-3-CHLORO-5, 5-DIMETHYLHYDANTOIN
[5,5-DIMETHYLHYDANTOIN]
SB 950-255, Chemical Code: 2080, Tolerance # 50272

August 5, 1986
Revised: 10/18/01

I. DATA GAP STATUS

Preliminary information: The following data gap status considers only data submitted on **1-Bromo-3-Chloro-5, 5-Dimethylhydantoin**; it does not reflect, test data sent in on the EPA-requested hydrolysis product of 5,5-Dimethylhydantoin. Studies received on 5,5-Dimethylhydantoin are indicated below.

Chronic, rat:	Data gap, no study on file (See 5,5-Dimethylhydantoin, 50433)
Chronic, dog:	Data gap, no study on file (See 5,5-Dimethylhydantoin, 50433)
Oncogenicity, rat:	Data gap, no study on file (See 5,5-Dimethylhydantoin, 50433)
Oncogenicity, mouse:	Data gap, no study on file (See 5,5-Dimethylhydantoin, 50433)
Reproduction, rat:	Data gap, inadequate study, (See 5,5-Dimethylhydantoin, below)
Teratology, rat:	Data gap, no study on file (See 5,5-Dimethylhydantoin, below)
Teratology, rabbit:	Data gap, no study on file (See 5,5-Dimethylhydantoin, below)
Gene mutation:	Data gap, inadequate study, no adverse effect indicated (See 5,5-Dimethylhydantoin, below)
Chromosome aberrations:	Data gap, no study on file (See 5,5-Dimethylhydantoin, below)
DNA damage:	Data gap, no study on file (See 5,5-Dimethylhydantoin, below)
Neurotoxicity:	Not required at this time

Note, Toxicology one-liners are attached
** indicates acceptable study
Bold face indicates possible adverse effect
Original: Indexed by C. Caraway; Toxicology summary prepared by J. Gee, 5/8/86.

Revised: J. Parker, 4/30/87; J.Gee, 5/29/87; M. Silva, 10/18/01
File Name: T011018

II. TOXICOLOGY SUMMARY

CHRONIC

No study on file

ONCOGENICITY

No study on file

REPRODUCTION

No study on file (See 5,5-Dimethylhydantoin for study)

TERATOLOGY

No study on file (See 5,5-Dimethylhydantoin for study)

MUTAGENICITY, GENE

50272 - 010 025012 (1977, LBI) Previously reviewed by JW on 6/28/85 in tandem with record number 010 025013. Both are mutagenicity assays, but record number 010 025013 reflects testing done on dimethylhydantoin and record number 010 025012 is on bromochlorodimethylhydantoin, therefore these two studies are not independent replicate studies, rather they are separate assays. JG re-reviewed this study on 8/8/86: 025012; 843-Muta-GNMU; bromo chlorodimethylhydantoin, no purity stated; tested at 0, 0.1, 1.0, 10.0, 100.0, 500.0 ul/plate with and without activation; *Salmonella*, 5 strains, no increase in reversion rate; one trial, one plate. Incomplete, unacceptable.

50272 - 006 025010 (1977, LBI) Duplicate of 50272 - 010 025012; "025012" has an additional page describing the test article.

MUTAGENICITY, CHROMOSOME

No study on file (See 5,5-Dimethylhydantoin for study)

MUTAGENICITY, DNA

No study on file (See 5,5-Dimethylhydantoin for study)

NEUROTOXICITY, HEN

Not required at this time.

EPA ONE-LINERS: No EPA one-liners available as of May 29, 1987.

5,5-DIMETHYLHYDANTOIN

EPA requested that testing be conducted on 5,5-Dimethylhydantoin, the hydrolysis product of the swimming pool disinfectant 1-Bromo-3-Chloro-5,5-Dimethylhydantoin (Chemical Code #: 2080, DPN #: 50272, SB 950 #: 255). See the letter dated September 11, 1985 in volume 50272 - 014.

I. DATA GAP STATUS

Combined (Chronic/Oncogenicity), rat:	No data gap, no adverse effect
Chronic, dog:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosomal aberrations:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Note, Toxicology one-liners are attached
** indicates acceptable study
Bold face indicates possible adverse effect
Original: Indexed by C. Caraway; Toxicology summary prepared by J. Gee, 5/8/86.
Revised: J. Parker, 4/30/87; J.Gee, 5/29/87; M. Silva, 10/18/01
File Name: T011018

50272 – 071 A letter from Lonza Inc. (8/18/92) provided information on halohydantoin products for water treatment. Chlorine and/or bromine components in water form hyperchlorous and hyperbromous acids and a hydantoin ring. The U.S. EPA stated that adequate data were available for hyperchlorous and hyperbromous acids and therefore, no further testing was required. "The hydantoin ring is not fully characterized and is, therefore, the test compound for the Data Call-In and Re-registration. Specifically, it

has been decided that the dimethylhydantoin (DMH) ring will be the test compound."

Halohydantoin products (see table below):

1. Bromo-3-chloro-5,5-dimethylhydantoin (DMH)
2. Dichloro-5,5-dimethylhydantoin (DMH)
3. Dibromo-5,5-dimethylhydantoin (DMH)

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC/ONCOGENICITY COMBINED, RAT

** 50433 - 006 132668 "Chronic Dietary Toxicity/Oncogenicity Study with 5,5-Dimethylhydantoin (DMH) in Rats," (Hermansky, S.J., Benson, C.L.; Bushy Run Research Center (BRRC), Export, PA; Laboratory Project ID #: 91N0113; 8/31/94). Dantoin® (DMH, purity = 99.8%) was fed in diet to CD® rats (60/sex/dose) at 0 (2 control groups), 100, 300, or 1000 mg/kg/day for 104 weeks. Diets were adjusted periodically for DMH concentration to maintain the doses with separate diets for males and females. Chronic NOEL = 300 mg/kg/day (Survival time relative to controls was decreased in both sexes at 1000 mg/kg/day, however it was statistically significantly decreased only in males. Bodyweights were statistically significantly lower (9 - 14%) in females at 1000 mg/kg late in the study. Bodyweight gains were significantly decreased (compared to both controls) in males at 1000 mg/kg. No effects were observed in relation to hematology, clinical chemistry, urinalysis, ophthalmology, organ weights or pathology.) Oncogenic NOEL > 1000 mg/kg/day (There were no treatment-related tumorigenic effects at any dose.) No adverse effect. Acceptable. (Kishiyama & Silva, 9/25/01).

** 50272 - 091 148862 "Combined 24-Month Toxicity/Oncogenicity Study in Rats with DMH," (Naas, D.J.; WIL Research Laboratories, Inc., Laboratory Study #: WIL-12258; 7/30/96). 5, 5-Dimethylhydantoin (DMH, purity = 93.5-97.3%) was fed in diet to Crl:CD®BR rats (80/sex/dose) at 0, 100, 320 and 1000 mg/kg/day for 104 weeks to test for DMH oncogenicity. In a chronic aspect of the study, rats (20/sex/dose) were sacrificed at 52 weeks. There were a total of 100/sex/dose at initiation of study. **Chronic NOEL =** 100 mg/kg/day (There was an increased incidence in wet and dried yellow matting urogenital area, primarily in males at $\geq$ 320 mg/kg.) There were no treatment-related effects in hematology, clinical chemistry, urinalysis, ophthalmology or histopathology. **Oncogenicity NOEL** > 1000 mg/kg (There were no treatment-related oncogenic effects at any dose.) ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 9/17/01).

Subchronic Study:

50272 – 033 048977: "90 Day Rat Oral Toxicity" (Stillmeadow, Inc., 9/5/86); 97% 5,5-Dimethylhydantoin (lot no. 0508LK) at doses of 1.0, 100 and 1050 mg/kg was administered to 20 rats/sex/group in 4 ml water by gavage 5 times per week. Comparable body weight gain, food consumption, hematology and clinical chemistry for all groups. NOEL >1<100 mg/kg/day. Not an SB950 required study. No adverse effect indicated. JRG/RAM 5/14/87.

50272 - 032 047931 "90 Day Repeated Dose Oral Toxicity Study on EMH or DMH" (Findley

Research, Inc., 7/24/86) DMH: lot no. 1083:32, 21.9%; purity not given for EMH; 0 or 1000 mg/kg/day DMH or EMH administered by aqueous gavage to 15/sex/group; One female died in EMH group. All others survived treatment. NOEL of DMH and EMH = 1000 mg/kg/day. Not an SB950 required study. (JSB) GT Patterson 1/20/87.

** 50272 - 078 129317 "Ninety-Day Dermal Toxicity Study with 5,5-Dimethylhydantoin (DMH) in CD® Rats," (Chun, J.S., Loughran, K.A.; Bushy Run Research Center, Lab Project #: 92N1016; 3/10/94). DMH (99% pure) was dermally administered to CD® rats (15/sex/dose) at 0, 39, 130 or 390 mg/kg/day (6 hours/day, 5 days/week) for 13 weeks. The treatment area was occluded with a gauze pad, covered with VETRAP® Bandaging tape during the 6-hour exposure period. Authors report DMH concentration greater than 13% exceeded water solubility. NOEL > 390/mg/kg/day (There were no DMH treatment-related systemic toxicity or dermal irritation effects at any dose in CD® rats.) The high dose (390 mg/kg/day) did not show evidence of treatment related toxicity (no MTD). However, the treatment solutions were saturated at the high dose and therefore it was not possible to administer a higher dose than was used. ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 9/10/01).

CHRONIC, DOG

** 50433 - 008 134528 "Evaluation of Dimethylhydantoin (DMH) in a One-Year Chronic Dietary Toxicity Study in Dogs," (Goldenthal, E.I.; International Research and Development Corporation, Mattawan, MI; Laboratory Product ID #: 647-004; 1/6/95). Dimethylhydantoin (purity = 98.9%) was fed in diet to Beagle dogs (4/sex/dose) at 0, 4000, 12000 and 40000 ppm for one-year. Chronic NOEL = 12000 ppm (Adrenal cortical hypertrophy was increased and correlated with increased relative adrenal weight for males at 40000 ppm. Adrenal hypertrophy was diffuse/bilateral and involved zona fasciculata cells. Body weight values were not statistically significantly decreased, but were generally lower in both sexes at 40000 ppm relative to the controls.) No adverse effects. NOEL = 12000 ppm. ACCEPTABLE. (Kishiyama & Silva, 9/19/01).

** 50272-086 140337 "One-Year Oral Toxicity Study in Dogs with DMH," (Chengelis, C.P.; WIL Research Laboratories, Inc., Ashland, OH; Laboratory Study #: WIL-12274; 3/14/95). 5, 5-Dimethylhydantoin (DMH purified, purity = 98.0 - 99.9%) was administered to Beagle dogs (4/sex/dose) in capsules at 0 (empty gelatin capsule), 250, 500 or 1000 mg/kg/day (limit test), once daily for 52 weeks. No treatment related effects were observed at any dose. NOEL > 1000 mg/kg/day. ACCEPTABLE (no MTD, but the limit test was used without toxicity). (Kishiyama & Silva, 12/14/01).

ONCOGENICITY, RAT

See Chronic/Oncogenicity, rat.

ONCOGENICITY, MOUSE

** 50433 - 005 132667 "Chronic Dietary Oncogenicity Study with 5,5-Dimethylhydantoin (DMH) in CD-1® Mice," (Hermansky, S.J., Loughran, K.A.; Bushy Run Research Center (BRRC), Export, PA; Laboratory Project ID #: 91N0112; 8/31/94). Dantoin® (purity = 99.8%) was fed in diet to CD-1® mice (60/sex/dose) at 0 (2 control groups = 120/sex total), 100, 300 or 1000 mg/kg/day for 78 weeks. Diets

were adjusted periodically for concentration to maintain doses with separate diets for males and females. Systemic NOEL = 300 mg/kg/day (Male bodyweights were decreased and amyloidosis increased in females at 1000 mg/kg.) Oncogenicity NOEL > 1000 mg/kg/day (There were no treatment-related oncogenic effects on study.) ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 9/21/01).

** 50272 - 089 148111 "18-Month Dietary Oncogenicity Study in Mice with DMH," (Naas, D.J.; WIL Research Laboratories, Ashland, OH; Study #: WIL-12257; 5/23/96). Dimethylhydantoin (purity = 97-99%) was fed in diet to Crl:CD-1®(ICR)BR mice (80sex/dose) at 0, 100, 320 and 1000 (Limit Test) mg/kg/day for 18 months. Systemic NOEL = 320 mg/kg (Body weights were only slightly decreased (5%), compared to control in males at 1000 mg/kg. Increased food consumption occurred primarily during weeks 58 through 69 in both sexes at 1000 mg/kg.) Oncogenicity NOEL > 1000 mg/kg (There were no treatment-related oncogenicity effects.) No adverse effects. ACCEPTABLE. (Kishiyama & Silva, 10/25/01).

REPRODUCTION, RAT

** 50433 - 007 132672 "Two-Generation Reproduction Study in CD® Rats with 5,5-Dimethylhydantoin (DMH) Administered in the Diet," (Neeper-Bradley, T.L., Kubena, M.F.; Bushy Run Research Center (BRRC), Export, PA; Laboratory Project ID 91N0094; 6/16/94). Dantoin (DMH, purity = 99.8%) was fed in diet to CD-1® rats (28/sex/dose/generation) at 0, 2000, 6000 or 20000 ppm (high dose for each generation exceeded the 1000 mg/kg limit test) for 2 generations. Exposure was for 10 weeks starting with F0 adult pre-mating, mating, gestation, parturition and lactation through F2 pup weaning. Parental Systemic NOEL = 6000 ppm (Food consumption was increased in both sexes at 20000 ppm at pre-mating. Body weights in F_0 males were slightly increased at 20000 ppm at pre-mating.) **Reproduction NOEL** > 20000 ppm (There were no treatment-related reproductive effects at any dose.) **Pup NOEL** = 6000 ppm (F_1 and F_2 pup body weights and body weight gains were significantly decreased during lactation at days 14, 21 and 28 [F_1] at 20000 ppm). ACCEPTABLE. No adverse effects. (Kishiyama & Silva, 10/3/01).

** 50272 - 079 130067 "Two-Generation Reproduction Study of Dimethylhydantoin Administered Orally in Rats," (Nemec, M.D.; WIL Research Laboratories, Inc., Laboratory Study #: WIL-12153; 7/24/92). Dimethylhydantoin (96.0 - 98.7% pure) was administered orally by gavage to Crl:CD®BR rats (30/sex/dose/generation) at 0 (1% methylcellulose), 250, 500 or 1000 mg/kg/day (limit test) from 70 days pre-mating through lactation (21 days post-natal) for 2 generations (F_0 & F_1). Reproductive NOEL > 1000 mg/kg/day (No treatment-related effects at any dose.) Pup NOEL = 250 mg/kg/day (F_1 pups had significantly decreased body weights at $\geq$ 500 mg/kg and F_2 pups at 1000 mg/kg. F_2 mean live litter size was significantly decreased at 1000 mg/kg prior to culling.) Male Parental NOEL = 250 mg/kg/day (F_1 weanling mean male body weights were decreased at the start of the F_1 generation. They were decreased 9-10% weeks 19 and 20 at $\geq$ 500 mg/kg and remained slightly decreased through week 37. These decreases were very slight, however (< 10%). Absolute and relative kidney (F_0) and pituitary (F_1) weights were increased in males at 1000 mg/kg.) Female Parental NOEL >1000 mg/kg/day (No treatment-related effects were observed at any dose.) ACCEPTABLE. No adverse effects. (Kishiyama & Silva, 10/18/01).

TERATOLOGY, RAT

There were no studies submitted under DPN #: 50433.

** 50272-071 117270 "Developmental Toxicity Evaluation of 5,5-Dimethylhydantoin (DMH) Administered by Gavage to CD® Rats," (Driscoll, C.D., Neeper-Bradley, T.L.; Bushy Run Research Center (BRRC), Export, PA; Laboratory Project ID #: 91N0048; 7/30/92). 5,5-dimethylhydantoin (purity = 99.8%) was administered to mated CD® rats (25/dose) via gavage at 0 (Milli-Q® filtered water), 100, 300 or 1000 mg/kg/day (limit test) on gestation days 6 through 15. Maternal NOEL > 1000 mg/kg/day and Developmental NOEL > 1000 mg/kg/day. No adverse effects. ACCEPTABLE. (Kishiyama & Silva, 9/13/01).

50272 - 018 036792 "A Range-Finding Teratology Study in Rats with 5,5-Dimethylhydantoin". (Wil Research Laboratories, Inc. Report # WIL-12001, 12-21-82, conducted for Great Lakes Chemical Corporation) 5,5-Dimethylhydantoin (890 00 00) ~ 100% was administered by gavage in 0.5% aqueous methylcellulose to groups of 5 mated Sprague-Dawley rats on gestation days 6 - 19 at dose levels of 0, 1.0, 2.5, 5.0, 7.5, and 10.0 g/kg/day. Clinical signs of toxicity (lethargy and ataxia) were observed at doses above 5.0 g/kg/day. There was 1 death at 7.5 g/kg/day and 2 deaths at 10.0 g/kg/day. There was no apparent effect on the number of implantations or resorptions. Data on clinical observations and necropsy observations are not presented. A high dose level of 4500 mg/kg/day was selected for the teratology study (018 36793). This is apparently justified and is far in excess of the EPA "limit" test. (Parker, 4-16-86 and 4-24-87).

50272 - 018 036793 "A Teratology Study in Rats with 5,5-Dimethylhydantoin, Project WIL-12002", (WIL Research Laboratories, Inc., 1-5-83, conducted for Great Lakes Chemical Corporation.) 5,5-Dimethylhydantoin (99.8% purity) in 0.5% methylcellulose was administered by gavage to Sprague-Dawley rats (25/group) at levels of 0, 500, 2000 or 4500 mg/kg/day on days 6 - 19 of gestation. Initially reviewed as unacceptable and possible adverse effect since developmental toxicity was seen at a level below maternal toxicity, JAP, 4-16-86. Additional data (justification for dose volume, individual and summary clinical and necropsy observations and justification for MTD) supplied, Record 038 051354. Study remains unacceptable but upgradeable with submission of dosing information. Maternal NOEL (statistically significant reduction in weight gain) = Developmental NOEL (statistically significant decrease in mean fetal weight and increase in skeletal variants) = 500 mg/kg/day. UNACCEPTABLE but upgradeable with no adverse effect indicated. (Parker, 4-27-87).

50272 - 044 061665 This volume contains records on the amount of dimethylhydantoin weighed during teratology study (WIL Project 12002). No worksheet. (M. Silva, 10/19/01).

50272 - 032 047932 "Developmental toxicity study in rats on EMH and DMH: limit test - TSCA Guidelines." (Findley Research, Inc., study no. T86M0006G, 8-12-86) 5,5-Dimethylhydantoin, lot 1083:32 and EMH, lot 1083:31, no purity stated; dose levels: vehicle - water, O mg/kg; EMH-1000, mg/kg; DMH-1000, mg/kg; and 6-AN at 3 and 10 mg/kg; EMH and DMH by gavage administered to groups of 22 or 23 mated Sprague-Dawley rats on days 6-15 of gestation. **Possible adverse effect (Developmental NOEL < 1000, increased incidence of skeletal variants, 14th ribs, with EMH and DMH;** with Maternal NOEL > 1000 mg/kg) UNACCEPTABLE (need historical control data for Findley Research Institute), upgradeable. (Berliner, 1/21/87 and Parker, 1/29/87).

Conclusion on rat teratology: In considering both rat teratology studies, more weight is given to record

36793 with higher doses and more animals. Since this study failed to identify a possible adverse effect (Maternal Toxicity NOEL = Developmental Toxicity NOEL) the conclusion is that DMH does not appear to be a hazard to developing rats. The data gap remains, however, until one of the studies is upgraded. (Parker 5/27/87).

TERATOLOGY, RABBIT

There were no studies submitted under DPN #: 50433.

**50272-033 48976 "Rabbit Teratogenicity Study". (Stillmeadow, Inc, 7-30-86, Project 3866-85) 5,5-Dimethylhydantoin (97%) was administered by gavage to groups of 27 mated New Zealand White Rabbits at dose levels of 0, 1.0, 100 or 1050 mg/kg/day in vehicle - water on days 7 - 19 of gestation. Possible increases in abortion rate and increased incidence of clinical signs at 1050 mg/kg/day, however not statistically significant. No evidence of toxicity in any fetal parameter measured. Maternal NOEL = Developmental NOEL = 1050 mg/kg/day. EPA "limit" test is 1000 mg/kg/day. Acceptable, no adverse effect. Parker, 5-4-87.

50272-032 47930 "Developmental toxicology study in rabbits on EMH and DMH limit test - TSCA Guidelines." (Findley Research, Inc., report T86M0007G, 8-6-86) DMH and EMH, no purity stated; administered by gavage to groups of 15 inseminated New Zealand White rabbits at O (water vehicle), EMH-1000 mg/kg, DMH-1000 mg/kg, 6-AN 3 mg/kg; gestation days 6-18; apparent increase in resorption rate with EMH and DMH, also decreased fetal wt. UNACCEPTABLE (needs historical control data), upgradeable with a **possible adverse effect indicated since no maternal toxicity was observed.** Maternal Toxicity NOEL > 1000 mg/kg. Developmental Toxicity NOEL < 1000 mg/kg. (Berliner, 1/20/87 and Parker, 1/29/87).

Conclusion on rabbit teratology: In considering both studies, more weight is given to 048976 with higher dose levels and more animals. No evidence of adverse effect is found, therefore, it is concluded that 5,5-Dimethylhydantoin is not a hazard to developing rabbits. (Parker, 5/27/87).

MUTAGENICITY, GENE

Bacterial systems

50673 - 008 039551 is an exact duplicate of 039253.

50272 - 010 025012 (1977, LBI) Previously reviewed by Wong on 6/28/85 in tandem with record #: 50272 - 010 025013. Both are mutagenicity assays, but record #: 50272 - 010 025013 reflects testing done on dimethylhydantoin and record number 010 025012 is on bromochlorodimethylhydantoin, therefore these two studies are not independent replicate studies, rather they are separate assays. Gee re-reviewed this study on 8/8/86: 025012; 843-Muta-GNMU; bromo chlorodimethylhydantoin, no purity stated; tested at 0, 0.1, 1.0, 10.0, 100.0, 500.0 ul/plate with and without activation; *Salmonella*, 5 strains, no increase in reversion rate; one trial, one plate. Incomplete, unacceptable.

50272 - 006 025010 (1977, LBI) Duplicate of 50272 - 010 025012; "-12" has one additional page which

describes the test article.

50272 - 010 025013. "Mutagenicity Evaluation of 277-24 - Final Report." (2/1977, Litton Bionetics, Project No. 2683) 5,5-Dimethylhydantoin, no purity stated; doses tested at 0, 0.1, 1.0, 100.0 or 500.0 ug/plate; *Salmonella,* five strains TA1535, TA1537, TA1538, TA98, TA100 and *Saccharomyces* D4; no increase in reversion rate; one trial, one plate. UNACCEPTABLE (no repeat trial, single plate per concentration, no rationale for not using a higher concentration.) Gee, 7/2/86.

50272 - 026 039253 "*Salmonella*/Mammalian-Microsome Preincubation Mutagenicity Assay (Ames Test) - Dimethylhydantoin". (9/3/1982, Microbiological Associates, Study No T1803.502) Dimethylhydantoin (no purity given); *Salmonella typhimurium* strains TA1535, TA1536, TA1538, TA98 and TA100, exposed during 20 minute preincubation in liquid to 100, 500, 2500, 5000 or 10,000 ug/plate final in 0.6 ml vol, with and without rat liver activation; single trial, triplicate plates. Incomplete (No repeat trial) therefore UNACCEPTABLE. (Gee, 1/14/86).

50673 - 008 039551 is an exact duplicate of 039253.

50272 - 033 048973 *"Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)." (Microbiological Associates, Inc., study no. T4638.501, 3/31/86) 5,5-Dimethylhydantoin, 97%, lot 0508LK; 0, 100, 500, 2500, 5000 or 10000 ug/plate with and without rat liver microsome activation in tester strains TA98, TA100, TA1535, TA1537 and TA1538; 3 replicates per plate and confirming experiment in TA1537 only. No dose dependent increase in reversion rate. No adverse effect indicated. UNACCEPTABLE (no repeat trial for all strains). (Marovich, 5/14/87).

50673 - 008 039550 "Mutagenicity Evaluation of Dimethyl Hydantoin 40-683 635658 in the Ames *Salmonella*/Microsome Plate Test: Final Report." (Litton Bionetics, 3/78, LBI Project No. 20838) Dimethyl hydantoin, white crystals, no purity or source stated, hydrolysis product of parent compound; tested at 0, 0.1, 1.0, 10, 100 or 500 ug/plate in strains TA1535, TA1537, TA1538, TA98 and TA100, and in *Saccharomyces cerevisiae* D4 at the same concentrations, with and without rat liver activation; UNACCEPTABLE (single plate, single trial, high concentration not justified), no increase in reversion rate at any concentration. (Gee, 3/13/86).

Mammalian systems

50272 - 015 036786 "Mouse Lymphoma Forward Mutation Assay - Dimethylhydantoin: Final Report." (10/29/1982, Hazleton Labs America, Project No. 224-102) Dimethylhydantoin (99.8%); with and without S-9 at 0, 82, 117, 240, 343, 490, 700 and 1000 ug/ml for 4 hours; no increase in mutation reported; UNACCEPTABLE (single trial). (Gee, 5/21/86 and 4/30/87).

50272 - 039 051355 Supplement to 036786 containing raw data and duplicate copy of final report.

50272 - 026 039256 "L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay - Dimethylhydantoin." (1/11/1983, Microbiological Associates, Study No. T1803.701001) Dimethylhydantoin (no purity given); with and without rat liver activation, 0 - 10,000 ug/ml at 10 concentrations of test agent; relatively non-cytotoxic; no increase in mutation frequency, one trial, therefore UNACCEPTABLE**.** (Gee, 1/16/86).

Summary: 50272 - 015 036786 and 50272 - 025 & 026 039259 represent, in essence, independent, repeat trials with mouse lymphoma with no evidence of forward mutation in a mammalian assay. The flaws in each study are minor other than the lack of a repeat trial. In addition, the *Salmonella* reports also serve to fulfill the repeat trial requirement, the major flaw in those studies. Considered collectively, there are sufficient data to determine whether dimethylhydantoin is mutagenic. **The data gap for gene mutation with 5,5-dimethylhydantoin can be considered filled with no adverse effect indicated.**

CHROMOSOME ABERRATION

There were no studies submitted under DPN #: 50433

50272 - 015 036787 "In vivo Bone Marrow cytogenetic Assay in Rats: 5,5-Dimethylhydantoin (DMH): Final Report." (10/26/1982, Hazleton Labs America, Project No. 224-103) Dimethylhydantoin, 99.8%; 3/sex/group given 0, 200, 660 or 2000 mg/kg by oral gavage and 3/sex/group sacrificed at 6, 12, 24 hours and 7 days (48 hours not analyzed). No effect on aberrations. Insufficient number of animals with cells from some not analyzed. Initially reviewed as unacceptable with no justification of dose selection. Comments in the rebuttal prepared by Hazleton in Document 50272-039 state the selection was similar to the highest dose in the 90-day subchronic study. There remains no evidence of an MTD or of bone marrow cytotoxicity. Study remains UNACCEPTABLE and not upgradeable. (Gee, 5/21/86 and 4/29/87).

50272 - 039 052054 Supplement to 036787. Raw data for study.

** 50272 - 026 039254 "Cytogenicity Study - Chinese Hamster Ovary (CHO) Cells *In Vitro*: Dimethylhydantoin. " (9/3/1982, Microbiological Associates, Study No. T1803.338). Dimethylhydantoin (purity not given); Chinese hamster ovary cells exposed for 4 hours in suspension to 0, 8457, 11,250 or 15,000 ug/ml with and without rat liver activation; after plating 16 hours plus 2 hours with colcemid, mitotic cells were harvested; no increase in aberrations is reported in 50 cells/culture/concentration. Initially reviewed as unacceptable (single culture, no confirming trial, no description of a.i.). The study was upgraded to ACCEPTABLE with justification for using the hydrolysis product and characterization of the test article. (Gee, 1/16/86 and 1/28/87)

50673 - 008 039557 Exact duplicate of 039254.

** 50272 - 033 048974 "Chromosome Aberration Assay in Chinese Hamster Ovary (CHO) Cells". (Microbiological Associates, Inc., study no. T4638.337, 4/4/86) 5,5-Dimethylhydantoin, 97%, lot 0508LK; 0, 100, 200, 500, 1000 or 2000 ug/ml with and without Aroclor-induced rat liver S-9 activation. Only top four doses were analyzed. No significant increase in numerical or structural chromosome aberrations were observed. No adverse effect indicated. ACCEPTABLE**.** (Gee and Marovich, 5/15/87).

MUTAGENICITY, DNA

There were no studies submitted under DPN #: 50433

** 50272 - 015 036788 "Cell Transformation Assay - Dimethylhydantoin with Metabolic Activation: Final

Report." (1/18/1983, Hazleton Labs America, Project No. 224-104) Dimethylhydantoin, 99.8%; C3H/10T 1/2 cells, pass 12, were exposed with S-9 for 5 hours to 0, 10, 30, 100, 300 or 1000 ug/ml; type III foci were scored; no increase with treatment was reported; 10 plates/concentration; one trial; initially reviewed as incomplete with only type III foci reported, S9 not described and no justification of high concentration used but upgradeable. With the submission of Record # 052055, raw data for the study, the deficiencies have been corrected and the study in conjunction with 036789 has been upgraded to ACCEPTABLE. (Gee, 5/21/86 and 4/30/87).

** 50272 - 015 036789 "Cell Transformation Assay - Dimethylhydantoin without Metabolic Activation: Final Report." (1/18/1983, Hazleton Labs. America, Project No.224-104). Cell transformation in C3H/10T 1/2, pass 12; dimethylhydantoin, 99.8%; treatment for 24 hours without activation at 0, 10, 30, 100, 300 or 1000 ug/ml 10/concentration; no increase in type III foci were reported; initially reviewed as incomplete (justification of high conc., only data on type III foci submitted, exposure conditions not clear), unacceptable - upgradeable. With the submission of Record # 052055, the deficiencies have been corrected and the study, in conjunction with 036788, is upgraded to ACCEPTABLE. (Gee, 5/21/86 and 4/30/87).

50272 - 039 052055 Raw data for 036788 and 036789.

** 50272 – 025 & 026 039255 "Unscheduled DNA Synthesis of Primary Culture of Rat Hepatocytes (By Autoradiography)". (10/29/1982, Microbiological Associates, Study No. T1803.380002) Dimethylhydantoin (no purity given); primary rat hepatocytes assayed for unscheduled DNA synthesis (UDS) following 18 hour exposure to 0, 1, 10, 100, 1000, 10,000 or 20,000 ug/ml medium ^{3}H-TdR incorporation into nuclei as grains by autoradiography; no increase in UDS with increasing conc. at cytotoxic levels. Initially reviewed as "Incomplete" (missing table 2, info), therefore unacceptable - upgradeable. The study was upgraded to ACCEPTABLE with submission of the missing table and characterization of the test article. (Gee, 1/15/86 and 1/28/87).

50673 - 008 039560 Exact duplicate of 039255.

** 50272 - 033 048975 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes; Final Report." (Microbiological Associates, Inc., study no. T4638.380, 5/5/86) 5,5-Dimethylhydantoin, 97%, lot 0508LK; 0, 10, 33, 67, 100, 333, 667, 1000, 3333, 6667 or 10000 ug/ml was applied to three replicate plates and incubated for 18-20 hours, with a parallel viability study. No significant increase in mean net nuclear counts. No adverse effect reported. ACCEPTABLE**.** (Marovich, 5/14/87).

NEUROTOXICITY, HEN

Not required at this time.

EPA ONE-LINERS: No EPA one-liners available as of July 1, 1986